Identification of the earliest natural killer cell committed progenitor in murine bone marrow.

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Public Summary:
Natural Killer (NK) cells are lymphocytes that provide a wide variety of protective functions against malignancies and viral infections. All lymphocytes, including, B cells, T cells, NK cells, and dendritic cells, are produced from Common Lymphocyte Progenitors (CLP). However, the developmental steps between CLP and the first NK committed cells remains unclear, hampering efforts to understand the mechanisms that regulate the development of this critical cell type. Using 12-color flow cytometry, we mapped the developmental stages between CLP and NK committed progenitors, and identified two major populations. One population is a subfraction of a previously identified progenitor called NKP. NKPs express a receptor for IL-15, a cytokine known to be critical for NK cell development. Our subfraction of NKP expresses several other surface markers, such as CD27, CD244, but does not express Flk2, a receptor expressed in CLP. Upon transplantation, this subfraction contains all the NK progenitor activity within the previously defined NKP population, suggesting that this fraction is the true NKP. We therefore nicknamed this population “rNKP”, for “refined NKP”. The second major population we identified, which we nicknamed “pre-NKP” appears to have a surface expression pattern that places it between CLP and rNKP. For example, it does not express the CLP marker Flk2, but also does not express the NKP-specific IL15 receptor. We show that in vitro, CLP generate NKP through a pre-NKP intermediate. Despite its similarity to CLP, pre-NKP produce only NK cells when transplanted in vivo, demonstrating that pre-NKP are a true NK committed progenitor. Also, because pre-NKP do not express the receptor for IL15, this suggests that IL15 signaling is not a prerequisite to NK commitment. We conclude that pre-NKP is the developmental intermediate that connects CLP to NKP, and thus is the earliest NK committed progenitor identified to date.

Scientific Abstract:
Natural killer (NK) cells develop in the bone marrow and are known to gradually acquire the ability to eliminate infected and malignant cells, yet the cellular stages of NK lineage commitment and maturation are incompletely understood. Using 12-color flow cytometry, we identified a novel NK-committed progenitor (pre-NKP) that is a developmental intermediate between the upstream common lymphoid progenitor (CLP) and the downstream NKP, previously assumed to represent the first stage of NK lineage commitment. Our analysis also refined the purity of NKPs (rNKP) by 6-fold such that 50% of both pre-NKP and rNKP cells gave rise to NKp46+ NK cells at the single cell level. Upon transplantation into unconditioned Rag2(-/-)Il2rgammac(-/-) recipients, both pre-NKPs and rNKPs generated mature NK cells expressing a repertoire of Ly49 family members that degranulated upon stimulation ex vivo. Intrathymic injection of these progenitors, however, yielded no NK cells, suggesting a separate origin of thymic NK cells. Unlike the rNKP, the pre-NKP does not express IL-2Rbeta (CD122), yet is lineage committed toward the NK cell fate, adding support to the theory that IL-15 signaling is not required for NK commitment. Taken together, our data provide a high-resolution in vivo analysis of the earliest steps of NK cell commitment and maturation.